Appeal Brief

Applicant(s)	Turner et al.
Application #	09/689,911
Date Filed	October 11, 2000
Title	Polynucleotides Encoding Human Galanin Family Proteins
Attorney Docket #	LEX-0068-USA
Group Art Unit	1647
Examiner	Bunner, Bridget E.

Filed in Triplicate

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Turner, Jr. *et al.*		
Serial No.:	09/689,911	Group Art Unit:	1647
Filed:	10/11/2000	Examiner:	B. Bunner
For:	Polynucleotides Encoding Human Galanin Family Proteins (As Previously Amended)	Attorney Docket No.:	LEX-0068-USA

APPEAL BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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APPEAL BRIEF

Sir:

Appellants hereby submit an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences ("the Board") in response to the Final Office Action mailed on May 5, 2003. The Notice of Appeal was timely submitted on September 5, 2003, and was received in the Patent and Trademark Office ("the Office") on September 11, 2003. This Appeal Brief is timely submitted in light of the concurrently filed Petition for an Extension of Time of three months to and including February 11, 2003, and authorization to deduct the fee as required under 37 C.F.R. § 1.17(a)(3) from Appellants' Representatives' deposit account. The Commissioner is also authorized to charge the fee for filing this Appeal Brief ($165.00), as required under 37 C.F.R. § 1.17(c), to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

Appellants believe no fees in addition to the fee for filing the Appeal Brief and the fee for the extension of time are due in connection with this Appeal Brief. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason related to this communication, the Commissioner is authorized to charge any underpayment or credit any overpayment to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

I. REAL PARTY IN INTEREST

The real party in interest is the Assignee, Lexicon Genetics Incorporated, 8800 Technology Forest Place, The Woodlands, Texas, 77381.

II. RELATED APPEALS AND INTERFERENCES

Appellants know of no related appeals or interferences.

III. STATUS OF THE CLAIMS

The present application was filed on October 11, 2000, claiming the benefit of U.S. Provisional

Application Number 60/158,848, which was filed on October 12, 1999, and included original claims 1-4. A First Official Action on the merits ("the First Action") was issued on March 11, 2002, in which the declaration and title of the application were objected to, claims 1-4 were rejected under 35 U.S.C. § 101 as allegedly lacking a patentable utility, claims 1-4 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, claims 1 and 4 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly not providing enablement for the full scope of the claimed invention, claims 1 and 4 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, claims 1, 2 and 4 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite, and claims 1 and 4 were rejected under 35 U.S.C. § 102(a), as allegedly anticipated by Zhao *et al.* (GenBank Accession Number AQ549952). In a response to the First Official Action submitted to the Office on July 1, 2002 ("Response to the First Action"), Appellants provided a supplemental declaration, amended the title of the application, amended claims 1, 2 and 4 to even further improve their clarity, added new claims 5-8, and addressed the rejections of claims 1-4.

A Second Official Action ("the Second Action") was mailed on September 24, 2002, indicating that the objection to the title of the application, and the rejection of claims 1 and 4 under 35 U.S.C. § 112, first paragraph, as allegedly not providing enablement for the full scope of the claimed invention, claims 1 and 4 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, claims 1 and 4 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite, and claims 1 and 4 under 35 U.S.C. § 102(a), as allegedly anticipated by Zhao *et al.* (GenBank Accession Number AQ549952), had been overcome by the amendments and remarks submitted in the Response to the First Action, but objecting to the supplemental declaration, and maintaining the rejection of claims 1-4 (and newly added claims 5-8) under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, and

claim 2 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In a response to the Second Action submitted on February 21, 2003 ("Response to the Second Action"), Appellants submitted a new supplemental declaration, amended claim 2 to even further improve its clarity, and addressed the rejections of claims 1-8.

A Third and Final Official Action ("the Final Action") was mailed on May 5, 2003, indicating that the objection to the declaration, and the rejection of claim 2 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite, had been overcome by the amendments and remarks submitted in the Response to the Second Action, but maintaining the rejection of claims 1-8 under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility. In a response to the Final Action submitted on September 5, 2003 ("Response to the Final Action"), Appellants again addressed the rejections of claims 1-8.

An Advisory Action ("the Advisory Action") was mailed on October 16, 2003, maintaining the rejection of claims 1-8 under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility. Therefore, claims 1-8 are the subject of this appeal. A copy of the appealed claims are included below in the Appendix (Section IX).

IV. STATUS OF THE AMENDMENTS

As no amendments subsequent to the Final Action have been filed, Appellants believe that no outstanding amendments exist.

V. SUMMARY OF THE INVENTION

The present invention relates to Appellants' discovery and identification of novel human polynucleotide sequences that encode proteins sharing sequence similarity with animal galanins (see, at least, the specification at page 2, lines 5-7, and Section 5.1). The presently claimed polynucleotide sequences were obtained from human gene trapped sequence tags (specification at page 12, lines 4-5).

The specification details, at least at page 1, lines 32-36, that the presently claimed galanin family sequences are involved in a number of functions, including a role in "inflammation" (specification at page 1, line 34). The specification as originally filed additionally states that "(t)he invention encompasses ... genetically engineered animals that either lack or over express (*sic*) the disclosed sequences" (specification at page 1, lines 11-15), and that "(t)he invention also encompasses ... transgenic animals that express a NHP transgene, or 'knock-outs' (which can be conditional) that do not express a functional NHP" (specification at page 2, lines 17-28).

The specification details a number of additional uses for the presently claimed polynucleotide sequences, including expression profiling using a high throughput "chip" format (specification at page 5, lines 2-4), and in determining the genomic structure, for example through the identification of coding sequence, and mapping the sequences to a specific region of a human chromosome (specification at page 7, line 20).

VI. ISSUES ON APPEAL

1. Do claims 1-8 lack a patentable utility?
2. Are claims 1-8 unusable by a skilled artisan due to a lack of patentable utility?

VII. GROUPING OF THE CLAIMS

For the purposes of the outstanding rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph concerning utility, the claims will stand or fall together.

VIII. ARGUMENT

A. Do Claims 1-8 Lack a Patentable Utility?

The Final Action next rejects claims 1-8 under 35 U.S.C. § 101, as allegedly lacking a patentable utility due to not being supported by either a specific and substantial utility or a well-established utility.

Appellants first point out that the presently claimed sequence shares 100% identity at the amino acid level with the first 98 amino acids of a sequence that is described in a journal article by Ohtaki *et al.*

(*J. Biol. Chem.* **274**:37041-37045. 1999), which was made of record in the present case by the Examiner in the First Action, as "Human Galanin-like Peptide (GALP)". Importantly, these scientists have functionally characterized GALP, detailing that the processed porcine GALP (1-60) preferentially binds and activates the galanin receptor GALR2 relative to GALR1 (see page 37045), and further, that the amino acid sequences surrounding the – and C-terminal processing sites lie within the first 85 amino acids of GALP and are conserved between the human and porcine GALP (see Fig. 3, page 37044). Appellants point out that the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. Given the significant homology between the presently claimed sequence and the human GALP sequence described by Ohtaki *et al.*, there can be **no question** that those skilled in the art would clearly believe that Appellants' sequence is a galanin family sequence, exactly as asserted by Appellants in the specification as originally filed.

Appellants respectfully point out that the present situation appears to directly track Example 10 of the Revised Interim Utility Guidelines Training Materials, which clearly establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility (see Section VIII(B), below), is not proper when a full length sequence (such as the presently claimed sequence) has a similarity score greater than 95% to a protein having a known function (such as the 100% identity between the presently claimed sequence and the mature human GALP sequence described and characterized by Ohtaki *et al.*, as discussed above). Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Furthermore, in the Response to the Second Action, Appellants noted that the specification as originally filed indicates that the presently claimed galanin family sequences are involved in a number of functions, including a role in "inflammation" (specification at page 1, line 34). Appellants also pointed out that this phenotype was confirmed in genetically engineered mice that lack the murine homolog of the presently claimed sequence (support for such "knockout" mice can be found, for example, in the specification at page 1, lines 11-15, and page 2, lines 17-28). Appellants pointed out that knockout mice

had been created in which a portion of the murine homolog of the presently claimed sequence was deleted. The knockout mice were then subjected to a well known peritoneal inflammation assay, which involves injection of the mice with zymosan, an extract of yeast cells. Appellants stated that the homozygous knockout animals showed an increase in total white blood cells compared to a wild-type control, consistent with, as set forth in the instant application, the stated role of this protein in inflammation. Thus, Appellants asserted that the present claims clearly meet the requirements of 35 U.S.C. § 101.

In the Final Action, the Examiner stated that this asserted utility "is credible, but not specific or substantial" (the Final Action at page 3). The Examiner set forth a number of arguments why Appellants' asserted utility is not "specific or substantial". First, the Examiner stated that "(t)he specification does not specifically disclose the generation of knockout mice lacking the murine homolog of the claimed polynucleotide" (the Final Action bridging pages 3 and 4). Appellants respectfully disagreed, and pointed out that the specification as originally filed clearly states that "(t)he invention encompasses ... genetically engineered animals that either lack or over express (*sic*) the disclosed sequences" (specification at page 1, lines 11-15), and that "(t)he invention also encompasses ... transgenic animals that express a NHP transgene, or 'knock-outs' (which can be conditional) that do not express a functional NHP" (specification at page 2, lines 17-28). Thus, the broad class of knockout animals, which by definition includes knockout mice, lacking the orthologous sequence that corresponds to the claimed sequence are clearly supported by the specification as originally filed. Furthermore, Appellants pointed out that the fact that the specification does not specifically single out knockout mice, while potentially relevant to written description questions, is irrelevant to the utility issue at hand. Therefore, the Examiner's argument does not support the alleged lack of utility.

Second, the Examiner stated that "(t)he specification also does not disclose subjecting the knockout animals to intraperitoneal inflammation assays to assess the immune system challenge with zymosan" (the Final Action at page 4). Appellants respectfully pointed out that the zymosan assay is well known to those of skill in the art, having been in use for well over 20 years (see, for example, Barrios *et al.*, *Am. J. Pathol.* **99**:731-740, 1980; a copy of the abstract previously submitted by Appellants in the Response to the Final Action provided in **Exhibit A**). Appellants pointed out that, as a matter of law, it is well settled

that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988). Therefore, this argument also does not support the alleged lack of utility.

Third, the Examiner argued that "(t)he specification does not teach any diseases or conditions (particularly inflammation) that are associated with a mutated, deleted, or translocated gene of the instant application" (the Final Action at page 4). Once again, Appellants respectfully disagreed, and pointed out that the specification as originally filed clearly states that the presently claimed sequence (also referred to in the specification as a NHP) is a galanin protein (see, at least, the specification at page 1, lines 10-11, page 2, lines 5-11, and Section 5.1), that "galanins have been associated with ... inflammation" (specification at page 1, lines 32-33), and, more directly, that "a mutant NHP allele" can result in "a NHP-associated phenotype such as ... an inflammatory disorder" (specification from page 8, line 37 to page 9, line 2). Thus, once again, the Examiner's argument does not support the alleged lack of utility.

Therefore, as the physiological role of the presently claimed sequence in inflammation, as set forth in the specification as originally filed, has been confirmed by Appellants in knockout animals that lack the orthologous sequence corresponding to the claimed sequence, which is clearly supported in the specification as originally filed, the present claims clearly meet the requirements of 35 U.S.C. § 101. Importantly, it has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974; "*Langer*"); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971). As set forth in *In re Langer* (183 USPQ 288 (CCPA 1974); "*Langer*"):

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer at 297, emphasis in original. As set forth in the MPEP, "Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art" (MPEP, Eighth Edition at 2100-40, emphasis added). Thus, absent such evidence from the Examiner concerning the role of the presently claimed sequence in inflammation, the present claims clearly

meet the requirements of 35 U.S.C. § 101.

Although Appellants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), Appellants pointed out in the Response to the First Action, the Response to the Second Action, and the Response to the Final Action that, given the obvious medical relevance of the presently claimed sequences, those of skill in the art would readily appreciate the importance of tracking the expression of the genes encoding the described proteins, as described in the specification as originally filed, at least at page 5, lines 2-4. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501, and 6,261,776. As the present sequences are specific markers of human chromosome 19 (see below), and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such DNA chips. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful.

Further, evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company (Rosetta Inpharmatics) was viewed to have such "real world" value that it was acquired by large a pharmaceutical company (Merck) for significant sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Thus, the present

sequence clearly meets the requirements of 35 U.S.C. § 101.

The Examiner also questioned this asserted utility, stating first that "the claimed polynucleotide is not disclosed as having a specific utility, or having any property ... that can be specifically useful" (the Final Action at page 5). As set forth in detail above, this is clearly not the case. Appellants have clearly asserted that the claimed sequence has a specific role in inflammation, and that the skilled artisan would readily understand that the identification of the physiological role of the claimed sequence in inflammation is certainly useful. The Examiner next stated that "use of the claimed polypeptide (*sic*) in an array for screening purposes is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array" (the Final Action at page 5). Appellants respectfully pointed out that nucleic acid sequences have the greatest specific utility in gene chip applications once the role of the sequence has been identified, as in the present case. Once the role of the particular nucleic acid is known, the level of gene expression has and even greater significance. By identifying the physiological role of the claimed sequence, specifically the role of the claimed sequence in inflammation, the claimed sequence has a far greater utility in gene chip applications that just any random piece of DNA.

The Examiner concluded that "this is a utility which (*sic*) would apply to virtually ever (*sic*) member of a general class of materials, such as any collection of proteins or DNA" (the Final Action at page 5). Appellants respectfully submit that this argument is flawed in a number of respects. First, Appellants point out that nucleic acid sequences are commonly used in gene chip applications without **any** information regarding the function of the encoded protein, or even evidence regarding whether the sequence is actually even expressed. Thus, the present sequence, which has been functionally characterized and biologically validated to be expressed, has a much greater utility than sequences that are merely predicted to be expressed based on bioinformatic analysis. Second, Appellants point out that nucleic acid sequences such as SEQ ID NO:1 are routinely used by companies throughout the biotechnology sector **exactly** as they are presented in the Sequence Listing, without **any** further experimentation. Expression profiling does **not** require a knowledge of the function of the particular nucleic acid on the chip - rather the gene chip indicates which DNA fragments are expressed at greater or lesser levels in two or more particular tissue types.

Third, as discussed above, as the physiological role of the presently claimed sequence has been set forth, the present sequence is not just any piece of DNA, as detailed above. Fourth, the Examiner appears to be confusing the requirement for a **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, with the requirement for a **unique** utility, which is clearly an improper standard. As clearly set forth by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Following directly from the quote above, an invention does not need to be the only way to accomplish a certain result. Thus, the question of whether or not other nucleic acid sequences can be used to assess gene expression using DNA chips is completely irrelevant to the present utility inquiry. The only relevant question in regard to meeting the standards of 35 U.S.C. § 101 is whether **every** nucleic acid can be so used - and the clear answer to this question is an emphatic **no**. Appellants point out that only a small percentage (2-4%) of the human genome actually encodes exon data, and these exons are widely interspersed within a given chromosome. Importantly, the holding in the *Carl Zeiss* case is **mandatory legal authority** that essentially controls the outcome of the present case. This case, and particularly the cited quote, **directly** rebuts the Examiner's argument. Furthermore, the requirement for a unique utility is clearly not the standard adopted by the Patent and Trademark Office. If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer and bacterial or viral infections, just to name a few particular examples, because examples of each of these have already been described and patented. All batteries have the exact same utility - specifically, to provide power. All automobile tires have the exact same utility - specifically, for use on automobiles. All golf balls and golf clubs have the exact same utility - specifically, use in the game of golf. All cancer treatments have the exact same utility - specifically, to treat cancer. All anti-infectious agents have the exact same broader utility - specifically, to treat infections. However, only the briefest perusal of virtually any issue of the Official

Gazette provides numerous examples of patents being granted on each of the above compositions every week. Additionally, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, *Science* **291**:1304, 2001). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, *Science* **291**:1153, 2001). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years). Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

As yet a further example of the utility of the presently claimed sequence, Appellants detailed in the Response to the Second Action and the Response to the Final Action that, as described in the specification at least at page 7, line 20, the present nucleotide sequence has a specific utility in determining the genomic structure of the corresponding human chromosome, for example mapping the protein encoding regions. This is evidenced by the fact that SEQ ID NO:1 can be used to map the 5 coding exons on human chromosome 19 (present within GenBank Accession Number AC024580, which is a genomic clone from human chromosome 19). A copy of the alignment and the first page from the GenBank report for AC024580, previously submitted by Appellants both in the Response to the Second Action and the Response to the Final Action, is provided in **Exhibit B**. In disclosing biologically validated exon splice junctions, the claimed sequence provides physical evidence that effectively trumps the hypothetical conclusions provided by bioinformatics analysis of the corresponding genomic region conducted without supporting physical data. Thus, the claimed sequence clearly meet the requirements of 35 U.S.C. § 101.

Appellants respectfully remind the Board that only a minor percentage of the genome (2-4%) actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Appellants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. Additionally, the specification details that "sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), *etc.*, that can be used in diagnostics and pharmacogenomics" (specification from page 7, lines 21-26). Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Additionally, the present nucleotide sequence has a specific utility in mapping the claimed sequence to the corresponding human chromosome, specifically chromosome 19, as described above. Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of human chromosome 19 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence. For further evidence in support of the Appellants' position, the Board is requested to review, for example, section 3 of Venter *et al.* (*supra*, at pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Examiner also questioned these asserted utilities, stating that "(s)uch assays can be performed with any polynucleotide" (the Final Action at page 7). First, Appellants respectfully point out that only those small percentage of nucleotide sequences that are located in this region of chromosome 19 can be used in such a manner, and not just "any polynucleotide". Second The Examiner once again seems to be confusing the requirements of a **specific** utility with a **unique** utility. The fact that a small number of other nucleotide sequences could be used to map the protein coding regions in this specific region of chromosome 19 does not mean that the use of Appellants' sequence to map the protein coding regions of chromosome 19 is not a specific utility (*Carl Zeiss Stiftung v. Renishaw PLC, supra*).

Rather, regarding the utility requirements under 35 U.S.C. § 101, the Federal Circuit has clearly stated "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 185 F.3d 1364, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable (*State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 149 F.3d 1368, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (U.S., 1980)). Thus, based on the relevant case law, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Additionally, regarding whether "extensive experimentation" (the Final Action at page 2) would be required to practice the claimed invention, Appellants point out that nucleic acid sequences such as SEQ ID NO:1 are routinely used by companies throughout the biotechnology sector **exactly** as they are presented in the Sequence Listing, without **any** further experimentation. In *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval

to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. Even if, *arguendo*, "further research" might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana*, which clearly states, as highlighted in the quote above, that "pharmaceutical inventions, necessarily includes the expectation of further research and development" (*Brana* at 1442-1443, emphasis added).

Furthermore, Appellants respectfully point out that the standard is not whether "extensive experimentation" is required, but, rather, whether **undue** experimentation is required. It is important to remember that in assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such

experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands, supra.*

Finally, While Appellants are well aware of the new Utility Guidelines set forth by the USPTO, Appellants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Appellants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Board is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotides), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section VIII(B), below), Appellants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Appellants agree that each application is examined on its own merits, Appellants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Appellants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, Appellants submit that the rejection of claims 1-8 under 35 U.S.C. § 101 must be overruled.

B. Are Claims 1-8 Unusable Due to a Lack of Patentable Utility?

The Final Action next rejects claims 1-8 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by either a clear asserted utility or a well-established utility.

The arguments detailed above in Section VIII(A) concerning the utility of the presently claimed sequences are incorporated herein by reference. As the Federal Circuit and its predecessor have determined that the utility requirement of Section 101 and the how to use requirement of Section 112, first paragraph, have the same basis, specifically the disclosure of a credible utility (*In re Brana*, *supra*; *In re Jolles*, 628 F.2d 1322, 1326 n.11, 206 USPQ 885, 889 n.11 (CCPA 1980); *In re Fouche*, 439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971)), Appellants submit that as claims 1-8 have been shown to have "a specific, substantial, and credible utility", as detailed in Section VIII(A) above, the present rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph, cannot stand.

Appellants therefore submit that the rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph, must be overruled.

IX. APPENDIX

The claims involved in this appeal are as follows:

1. (Previously Presented) An isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1.

2. (Previously Presented) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO: 2; and

(b) hybridizes to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof under highly stringent conditions of 0.5 M $NaHPO_4$, 7% sodium dodecyl sulfate (SDS) and 1 mM EDTA at 65°C and washing in 0.1x SSC/0.1%SDS at 68°C.

3. (Original) An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO: 2.

4. (Previously Presented) An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence from amino acid number 33 to amino acid number 141 of SEQ ID NO:2.

5. (Previously Presented) A recombinant expression vector comprising the nucleic acid molecule of claim 4.

6. (Previously Presented) The recombinant expression vector of claim 5, wherein the nucleic acid molecule comprises a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:2.

7. (Previously Presented) The recombinant expression vector of claim 6, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:1.

8. (Previously Presented) A host cell comprising the recombinant expression vector of claim 5.

X. CONCLUSION

Appellants respectfully submit that, in light of the foregoing arguments, the Final Action's conclusion that claims 1-8 lack a patentable utility and are unusable by the skilled artisan due to a lack of patentable utility, are unwarranted. It is therefore requested that the Board overturn the Final Action's rejections.

Respectfully submitted,

February 11, 2004
Date

David W. Hibler Reg. No. 41,071
Agent For Appellants

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8800 Technology Forest Place
The Woodlands, TX 77381
(281) 863-3399

TABLE OF AUTHORITIES

CASES

STATUTES

1: Am J Pathol. 1980 Jun;99(3):731-40. Related Articles, Links

Zymosan-induced experimental hypersensitivity pneumonitis in rabbits.

Barrios R, Santos GG, Figueroa J, Reyes PA.

An experimental model of hypersensitivity pneumonitis is presented. New Zealand white rabbits, previously immunized against yeast-derived zymosan, reacted to intratracheal challenge developing extensive pneumonitis. The lesions healed in a few weeks. Control animals challenged with inert particulate material (latex beads) or suspending fluid (PBS-Mg++) did not show pulmonary inflammation. Nonimmunized rabbits developed only transient pneumonitis after zymosan challenge. This reaction was clearly different from that seen in the group of immunized animals. The model reveals that biologically active substances such as zymosan, which is able to activate the alternate pathway of complement and mononuclear phagocytes, requires an active immune state in order to cause significant tissue damage. Isolated exposure to this kind of substance may not be sufficient to cause lung disease.

PMID: 7386601 [PubMed - indexed for MEDLINE]

Query= SEQ ID NO:1
(426 letters)

Sequences producing significant alignments:	Score (bits)	E Value
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Strand = Plus / Plus

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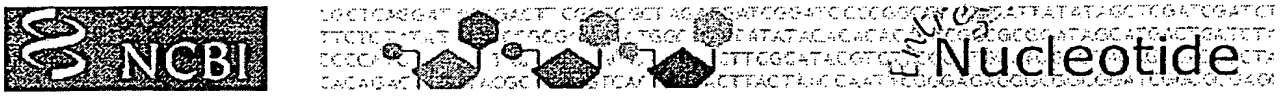

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ACCESSION   AC024580
VERSION     AC024580.6  GI:17975240
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  TITLE     Direct Submission
  JOURNAL   Unpublished
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  TITLE     Direct Submission
  JOURNAL   Submitted (29-FEB-2000) Production Sequencing Facility, DOE Joint
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  TITLE     Direct Submission
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            Drive, Walnut Creek, CA 94598, USA
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            Drive, Walnut Creek, CA 94598, USA
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            Finishing Completed at Stanford Human Genome Center
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Appeal Brief

Applicant(s)	Turner et al.
Application #	09/689,911
Date Filed	October 11, 2000
Title	Polynucleotides Encoding Human Galanin Family Proteins
Attorney Docket #	LEX-0068-USA
Group Art Unit	1647
Examiner	Bunner, Bridget E.

Filed in Triplicate

2 of 3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Turner, Jr. *et al.*		
Serial No.:	09/689,911	Group Art Unit:	1647
Filed:	10/11/2000	Examiner:	B. Bunner
For:	Polynucleotides Encoding Human Galanin Family Proteins (As Previously Amended)	Attorney Docket No.:	LEX-0068-USA

APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TABLE OF CONTENTS

APPEAL BRIEF

Sir:

Appellants hereby submit an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences ("the Board") in response to the Final Office Action mailed on May 5, 2003. The Notice of Appeal was timely submitted on September 5, 2003, and was received in the Patent and Trademark Office ("the Office") on September 11, 2003. This Appeal Brief is timely submitted in light of the concurrently filed Petition for an Extension of Time of three months to and including February 11, 2003, and authorization to deduct the fee as required under 37 C.F.R. § 1.17(a)(3) from Appellants' Representatives' deposit account. The Commissioner is also authorized to charge the fee for filing this Appeal Brief ($165.00), as required under 37 C.F.R. § 1.17(c), to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

Appellants believe no fees in addition to the fee for filing the Appeal Brief and the fee for the extension of time are due in connection with this Appeal Brief. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason related to this communication, the Commissioner is authorized to charge any underpayment or credit any overpayment to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

I. REAL PARTY IN INTEREST

The real party in interest is the Assignee, Lexicon Genetics Incorporated, 8800 Technology Forest Place, The Woodlands, Texas, 77381.

II. RELATED APPEALS AND INTERFERENCES

Appellants know of no related appeals or interferences.

III. STATUS OF THE CLAIMS

The present application was filed on October 11, 2000, claiming the benefit of U.S. Provisional

Application Number 60/158,848, which was filed on October 12, 1999, and included original claims 1-4. A First Official Action on the merits ("the First Action") was issued on March 11, 2002, in which the declaration and title of the application were objected to, claims 1-4 were rejected under 35 U.S.C. § 101 as allegedly lacking a patentable utility, claims 1-4 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, claims 1 and 4 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly not providing enablement for the full scope of the claimed invention, claims 1 and 4 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, claims 1, 2 and 4 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite, and claims 1 and 4 were rejected under 35 U.S.C. § 102(a), as allegedly anticipated by Zhao *et al.* (GenBank Accession Number AQ549952). In a response to the First Official Action submitted to the Office on July 1, 2002 ("Response to the First Action"), Appellants provided a supplemental declaration, amended the title of the application, amended claims 1, 2 and 4 to even further improve their clarity, added new claims 5-8, and addressed the rejections of claims 1-4.

A Second Official Action ("the Second Action") was mailed on September 24, 2002, indicating that the objection to the title of the application, and the rejection of claims 1 and 4 under 35 U.S.C. § 112, first paragraph, as allegedly not providing enablement for the full scope of the claimed invention, claims 1 and 4 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, claims 1 and 4 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite, and claims 1 and 4 under 35 U.S.C. § 102(a), as allegedly anticipated by Zhao *et al.* (GenBank Accession Number AQ549952), had been overcome by the amendments and remarks submitted in the Response to the First Action, but objecting to the supplemental declaration, and maintaining the rejection of claims 1-4 (and newly added claims 5-8) under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, and

claim 2 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In a response to the Second Action submitted on February 21, 2003 ("Response to the Second Action"), Appellants submitted a new supplemental declaration, amended claim 2 to even further improve its clarity, and addressed the rejections of claims 1-8.

A Third and Final Official Action ("the Final Action") was mailed on May 5, 2003, indicating that the objection to the declaration, and the rejection of claim 2 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite, had been overcome by the amendments and remarks submitted in the Response to the Second Action, but maintaining the rejection of claims 1-8 under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility. In a response to the Final Action submitted on September 5, 2003 ("Response to the Final Action"), Appellants again addressed the rejections of claims 1-8.

An Advisory Action ("the Advisory Action") was mailed on October 16, 2003, maintaining the rejection of claims 1-8 under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility. Therefore, claims 1-8 are the subject of this appeal. A copy of the appealed claims are included below in the Appendix (Section IX).

IV. STATUS OF THE AMENDMENTS

As no amendments subsequent to the Final Action have been filed, Appellants believe that no outstanding amendments exist.

V. SUMMARY OF THE INVENTION

The present invention relates to Appellants' discovery and identification of novel human polynucleotide sequences that encode proteins sharing sequence similarity with animal galanins (see, at least, the specification at page 2, lines 5-7, and Section 5.1). The presently claimed polynucleotide sequences were obtained from human gene trapped sequence tags (specification at page 12, lines 4-5).

The specification details, at least at page 1, lines 32-36, that the presently claimed galanin family sequences are involved in a number of functions, including a role in "inflammation" (specification at page 1, line 34). The specification as originally filed additionally states that "(t)he invention encompasses ... genetically engineered animals that either lack or over express (*sic*) the disclosed sequences" (specification at page 1, lines 11-15), and that "(t)he invention also encompasses ... transgenic animals that express a NHP transgene, or 'knock-outs' (which can be conditional) that do not express a functional NHP" (specification at page 2, lines 17-28).

The specification details a number of additional uses for the presently claimed polynucleotide sequences, including expression profiling using a high throughput "chip" format (specification at page 5, lines 2-4), and in determining the genomic structure, for example through the identification of coding sequence, and mapping the sequences to a specific region of a human chromosome (specification at page 7, line 20).

VI. ISSUES ON APPEAL

1. Do claims 1-8 lack a patentable utility?
2. Are claims 1-8 unusable by a skilled artisan due to a lack of patentable utility?

VII. GROUPING OF THE CLAIMS

For the purposes of the outstanding rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph concerning utility, the claims will stand or fall together.

VIII. ARGUMENT

A. Do Claims 1-8 Lack a Patentable Utility?

The Final Action next rejects claims 1-8 under 35 U.S.C. § 101, as allegedly lacking a patentable utility due to not being supported by either a specific and substantial utility or a well-established utility.

Appellants first point out that the presently claimed sequence shares 100% identity at the amino acid level with the first 98 amino acids of a sequence that is described in a journal article by Ohtaki *et al.*

(*J. Biol. Chem.* **274**:37041-37045. 1999), which was made of record in the present case by the Examiner in the First Action, as "Human Galanin-like Peptide (GALP)". Importantly, these scientists have functionally characterized GALP, detailing that the processed porcine GALP (1-60) preferentially binds and activates the galanin receptor GALR2 relative to GALR1 (see page 37045), and further, that the amino acid sequences surrounding the – and C-terminal processing sites lie within the first 85 amino acids of GALP and are conserved between the human and porcine GALP (see Fig. 3, page 37044). Appellants point out that the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. Given the significant homology between the presently claimed sequence and the human GALP sequence described by Ohtaki *et al.*, there can be **no question** that those skilled in the art would clearly believe that Appellants' sequence is a galanin family sequence, exactly as asserted by Appellants in the specification as originally filed.

Appellants respectfully point out that the present situation appears to directly track Example 10 of the Revised Interim Utility Guidelines Training Materials, which clearly establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility (see Section VIII(B), below), is not proper when a full length sequence (such as the presently claimed sequence) has a similarity score greater than 95% to a protein having a known function (such as the 100% identity between the presently claimed sequence and the mature human GALP sequence described and characterized by Ohtaki *et al.*, as discussed above). Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Furthermore, in the Response to the Second Action, Appellants noted that the specification as originally filed indicates that the presently claimed galanin family sequences are involved in a number of functions, including a role in "inflammation" (specification at page 1, line 34). Appellants also pointed out that this phenotype was confirmed in genetically engineered mice that lack the murine homolog of the presently claimed sequence (support for such "knockout" mice can be found, for example, in the specification at page 1, lines 11-15, and page 2, lines 17-28). Appellants pointed out that knockout mice

had been created in which a portion of the murine homolog of the presently claimed sequence was deleted. The knockout mice were then subjected to a well known peritoneal inflammation assay, which involves injection of the mice with zymosan, an extract of yeast cells. Appellants stated that the homozygous knockout animals showed an increase in total white blood cells compared to a wild-type control, consistent with, as set forth in the instant application, the stated role of this protein in inflammation. Thus, Appellants asserted that the present claims clearly meet the requirements of 35 U.S.C. § 101.

In the Final Action, the Examiner stated that this asserted utility "is credible, but not specific or substantial" (the Final Action at page 3). The Examiner set forth a number of arguments why Appellants' asserted utility is not "specific or substantial". First, the Examiner stated that "(t)he specification does not specifically disclose the generation of knockout mice lacking the murine homolog of the claimed polynucleotide" (the Final Action bridging pages 3 and 4). Appellants respectfully disagreed, and pointed out that the specification as originally filed clearly states that "(t)he invention encompasses ... genetically engineered animals that either lack or over express (*sic*) the disclosed sequences" (specification at page 1, lines 11-15), and that "(t)he invention also encompasses ... transgenic animals that express a NHP transgene, or 'knock-outs' (which can be conditional) that do not express a functional NHP" (specification at page 2, lines 17-28). Thus, the broad class of knockout animals, which by definition includes knockout mice, lacking the orthologous sequence that corresponds to the claimed sequence are clearly supported by the specification as originally filed. Furthermore, Appellants pointed out that the fact that the specification does not specifically single out knockout mice, while potentially relevant to written description questions, is irrelevant to the utility issue at hand. Therefore, the Examiner's argument does not support the alleged lack of utility.

Second, the Examiner stated that "(t)he specification also does not disclose subjecting the knockout animals to intraperitoneal inflammation assays to assess the immune system challenge with zymosan" (the Final Action at page 4). Appellants respectfully pointed out that the zymosan assay is well known to those of skill in the art, having been in use for well over 20 years (see, for example, Barrios *et al.*, *Am. J. Pathol.* **99**:731-740, 1980; a copy of the abstract previously submitted by Appellants in the Response to the Final Action provided in **Exhibit A**). Appellants pointed out that, as a matter of law, it is well settled

that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988). Therefore, this argument also does not support the alleged lack of utility.

Third, the Examiner argued that "(t)he specification does not teach any diseases or conditions (particularly inflammation) that are associated with a mutated, deleted, or translocated gene of the instant application" (the Final Action at page 4). Once again, Appellants respectfully disagreed, and pointed out that the specification as originally filed clearly states that the presently claimed sequence (also referred to in the specification as a NHP) is a galanin protein (see, at least, the specification at page 1, lines 10-11, page 2, lines 5-11, and Section 5.1), that "galanins have been associated with ... inflammation" (specification at page 1, lines 32-33), and, more directly, that "a mutant NHP allele" can result in "a NHP-associated phenotype such as ... an inflammatory disorder" (specification from page 8, line 37 to page 9, line 2). Thus, once again, the Examiner's argument does not support the alleged lack of utility.

Therefore, as the physiological role of the presently claimed sequence in inflammation, as set forth in the specification as originally filed, has been confirmed by Appellants in knockout animals that lack the orthologous sequence corresponding to the claimed sequence, which is clearly supported in the specification as originally filed, the present claims clearly meet the requirements of 35 U.S.C. § 101. Importantly, it has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974; "*Langer*"); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971). As set forth in *In re Langer* (183 USPQ 288 (CCPA 1974); "*Langer*"):

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer at 297, emphasis in original. As set forth in the MPEP, "Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art" (MPEP, Eighth Edition at 2100-40, emphasis added). Thus, absent such evidence from the Examiner concerning the role of the presently claimed sequence in inflammation, the present claims clearly

meet the requirements of 35 U.S.C. § 101.

Although Appellants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), Appellants pointed out in the Response to the First Action, the Response to the Second Action, and the Response to the Final Action that, given the obvious medical relevance of the presently claimed sequences, those of skill in the art would readily appreciate the importance of tracking the expression of the genes encoding the described proteins, as described in the specification as originally filed, at least at page 5, lines 2-4. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934, 5,556,752, 5,744,305, 5,837,832, 6,156,501, and 6,261,776. As the present sequences are specific markers of human chromosome 19 (see below), and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such DNA chips. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful.

Further, evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company (Rosetta Inpharmatics) was viewed to have such "real world" value that it was acquired by large a pharmaceutical company (Merck) for significant sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Thus, the present

sequence clearly meets the requirements of 35 U.S.C. § 101.

The Examiner also questioned this asserted utility, stating first that "the claimed polynucleotide is not disclosed as having a specific utility, or having any property ... that can be specifically useful" (the Final Action at page 5). As set forth in detail above, this is clearly not the case. Appellants have clearly asserted that the claimed sequence has a specific role in inflammation, and that the skilled artisan would readily understand that the identification of the physiological role of the claimed sequence in inflammation is certainly useful. The Examiner next stated that "use of the claimed polypeptide (*sic*) in an array for screening purposes is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array" (the Final Action at page 5). Appellants respectfully pointed out that nucleic acid sequences have the greatest specific utility in gene chip applications once the role of the sequence has been identified, as in the present case. Once the role of the particular nucleic acid is known, the level of gene expression has and even greater significance. By identifying the physiological role of the claimed sequence, specifically the role of the claimed sequence in inflammation, the claimed sequence has a far greater utility in gene chip applications that just any random piece of DNA.

The Examiner concluded that "this is a utility which (*sic*) would apply to virtually ever (*sic*) member of a general class of materials, such as any collection of proteins or DNA" (the Final Action at page 5). Appellants respectfully submit that this argument is flawed in a number of respects. First, Appellants point out that nucleic acid sequences are commonly used in gene chip applications without **any** information regarding the function of the encoded protein, or even evidence regarding whether the sequence is actually even expressed. Thus, the present sequence, which has been functionally characterized and biologically validated to be expressed, has a much greater utility than sequences that are merely predicted to be expressed based on bioinformatic analysis. Second, Appellants point out that nucleic acid sequences such as SEQ ID NO:1 are routinely used by companies throughout the biotechnology sector **exactly** as they are presented in the Sequence Listing, without **any** further experimentation. Expression profiling does **not** require a knowledge of the function of the particular nucleic acid on the chip - rather the gene chip indicates which DNA fragments are expressed at greater or lesser levels in two or more particular tissue types.

Third, as discussed above, as the physiological role of the presently claimed sequence has been set forth, the present sequence is not just any piece of DNA, as detailed above. Fourth, the Examiner appears to be confusing the requirement for a **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, with the requirement for a **unique** utility, which is clearly an improper standard. As clearly set forth by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Following directly from the quote above, an invention does not need to be the only way to accomplish a certain result. Thus, the question of whether or not other nucleic acid sequences can be used to assess gene expression using DNA chips is completely irrelevant to the present utility inquiry. The only relevant question in regard to meeting the standards of 35 U.S.C. § 101 is whether **every** nucleic acid can be so used - and the clear answer to this question is an emphatic **no**. Appellants point out that only a small percentage (2-4%) of the human genome actually encodes exon data, and these exons are widely interspersed within a given chromosome. Importantly, the holding in the *Carl Zeiss* case is **mandatory legal authority** that essentially controls the outcome of the present case. This case, and particularly the cited quote, **directly** rebuts the Examiner's argument. Furthermore, the requirement for a unique utility is clearly not the standard adopted by the Patent and Trademark Office. If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer and bacterial or viral infections, just to name a few particular examples, because examples of each of these have already been described and patented. All batteries have the exact same utility - specifically, to provide power. All automobile tires have the exact same utility - specifically, for use on automobiles. All golf balls and golf clubs have the exact same utility - specifically, use in the game of golf. All cancer treatments have the exact same utility - specifically, to treat cancer. All anti-infectious agents have the exact same broader utility - specifically, to treat infections. However, only the briefest perusal of virtually any issue of the Official

Gazette provides numerous examples of patents being granted on each of the above compositions every week. Additionally, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, *Science* **291**:1304, 2001). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, *Science* **291**:1153, 2001). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years). Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

As yet a further example of the utility of the presently claimed sequence, Appellants detailed in the Response to the Second Action and the Response to the Final Action that, as described in the specification at least at page 7, line 20, the present nucleotide sequence has a specific utility in determining the genomic structure of the corresponding human chromosome, for example mapping the protein encoding regions. This is evidenced by the fact that SEQ ID NO:1 can be used to map the 5 coding exons on human chromosome 19 (present within GenBank Accession Number AC024580, which is a genomic clone from human chromosome 19). A copy of the alignment and the first page from the GenBank report for AC024580, previously submitted by Appellants both in the Response to the Second Action and the Response to the Final Action, is provided in **Exhibit B**. In disclosing biologically validated exon splice junctions, the claimed sequence provides physical evidence that effectively trumps the hypothetical conclusions provided by bioinformatics analysis of the corresponding genomic region conducted without supporting physical data. Thus, the claimed sequence clearly meet the requirements of 35 U.S.C. § 101.

Appellants respectfully remind the Board that only a minor percentage of the genome (2-4%) actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Appellants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. Additionally, the specification details that "sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), *etc.*, that can be used in diagnostics and pharmacogenomics" (specification from page 7, lines 21-26). Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Additionally, the present nucleotide sequence has a specific utility in mapping the claimed sequence to the corresponding human chromosome, specifically chromosome 19, as described above. Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of human chromosome 19 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence. For further evidence in support of the Appellants' position, the Board is requested to review, for example, section 3 of Venter *et al.* (*supra*, at pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Examiner also questioned these asserted utilities, stating that "(s)uch assays can be performed with any polynucleotide" (the Final Action at page 7). First, Appellants respectfully point out that only those small percentage of nucleotide sequences that are located in this region of chromosome 19 can be used in such a manner, and not just "any polynucleotide". Second The Examiner once again seems to be confusing the requirements of a **specific** utility with a **unique** utility. The fact that a small number of other nucleotide sequences could be used to map the protein coding regions in this specific region of chromosome 19 does not mean that the use of Appellants' sequence to map the protein coding regions of chromosome 19 is not a specific utility (*Carl Zeiss Stiftung v. Renishaw PLC, supra*).

Rather, regarding the utility requirements under 35 U.S.C. § 101, the Federal Circuit has clearly stated "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 185 F.3d 1364, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable (*State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 149 F.3d 1368, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (U.S., 1980)). Thus, based on the relevant case law, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Additionally, regarding whether "extensive experimentation" (the Final Action at page 2) would be required to practice the claimed invention, Appellants point out that nucleic acid sequences such as SEQ ID NO:1 are routinely used by companies throughout the biotechnology sector **exactly** as they are presented in the Sequence Listing, without **any** further experimentation. In *In re Brana*, (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval

to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted. Even if, *arguendo*, "further research" might be required in certain aspects of the present invention, this does not preclude a finding that the invention has utility, as set forth by the Federal Circuit's holding in *Brana*, which clearly states, as highlighted in the quote above, that "pharmaceutical inventions, necessarily includes the expectation of further research and development" (*Brana* at 1442-1443, emphasis added).

Furthermore, Appellants respectfully point out that the standard is not whether "extensive experimentation" is required, but, rather, whether **undue** experimentation is required. It is important to remember that in assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such

experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands, supra.*

Finally, While Appellants are well aware of the new Utility Guidelines set forth by the USPTO, Appellants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Appellants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Board is invited to review U.S. Patent Nos. 5,817,479, 5,654,173, and 5,552,281 (each of which claims short polynucleotides), and recently issued U.S. Patent No. 6,340,583 (which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section VIII(B), below), Appellants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Appellants agree that each application is examined on its own merits, Appellants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Appellants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, Appellants submit that the rejection of claims 1-8 under 35 U.S.C. § 101 must be overruled.

B. Are Claims 1-8 Unusable Due to a Lack of Patentable Utility?

The Final Action next rejects claims 1-8 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by either a clear asserted utility or a well-established utility.

The arguments detailed above in Section VIII(A) concerning the utility of the presently claimed sequences are incorporated herein by reference. As the Federal Circuit and its predecessor have determined that the utility requirement of Section 101 and the how to use requirement of Section 112, first paragraph, have the same basis, specifically the disclosure of a credible utility (*In re Brana, supra*; *In re Jolles*, 628 F.2d 1322, 1326 n.11, 206 USPQ 885, 889 n.11 (CCPA 1980); *In re Fouche*, 439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971)), Appellants submit that as claims 1-8 have been shown to have "a specific, substantial, and credible utility", as detailed in Section VIII(A) above, the present rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph, cannot stand.

Appellants therefore submit that the rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph, must be overruled.

IX. APPENDIX

The claims involved in this appeal are as follows:

1. (Previously Presented) An isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 1.

2. (Previously Presented) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO: 2; and

(b) hybridizes to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof under highly stringent conditions of 0.5 M $NaHPO_4$, 7% sodium dodecyl sulfate (SDS) and 1 mM EDTA at 65°C and washing in 0.1x SSC/0.1%SDS at 68°C.

3. (Original) An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO: 2.

4. (Previously Presented) An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence from amino acid number 33 to amino acid number 141 of SEQ ID NO:2.

5. (Previously Presented) A recombinant expression vector comprising the nucleic acid molecule of claim 4.

6. (Previously Presented) The recombinant expression vector of claim 5, wherein the nucleic acid molecule comprises a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:2.

7. (Previously Presented) The recombinant expression vector of claim 6, wherein the nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:1.

8. (Previously Presented) A host cell comprising the recombinant expression vector of claim 5.

X. CONCLUSION

Appellants respectfully submit that, in light of the foregoing arguments, the Final Action's conclusion that claims 1-8 lack a patentable utility and are unusable by the skilled artisan due to a lack of patentable utility, are unwarranted. It is therefore requested that the Board overturn the Final Action's rejections.

Respectfully submitted,

February 11, 2004
Date

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TABLE OF AUTHORITIES

CASES

STATUTES

1: Am J Pathol. 1980 Jun;99(3):731-40.

Related Articles, Links

Zymosan-induced experimental hypersensitivity pneumonitis in rabbits.

Barrios R, Santos GG, Figueroa J, Reyes PA.

An experimental model of hypersensitivity pneumonitis is presented. New Zealand white rabbits, previously immunized against yeast-derived zymosan, reacted to intratracheal challenge developing extensive pneumonitis. The lesions healed in a few weeks. Control animals challenged with inert particulate material (latex beads) or suspending fluid (PBS-Mg++) did not show pulmonary inflammation. Nonimmunized rabbits developed only transient pneumonitis after zymosan challenge. This reaction was clearly different from that seen in the group of immunized animals. The model reveals that biologically active substances such as zymosan, which is able to activate the alternate pathway of complement and mononuclear phagocytes, requires an active immune state in order to cause significant tissue damage. Isolated exposure to this kind of substance may not be sufficient to cause lung disease.

PMID: 7386601 [PubMed - indexed for MEDLINE]

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Sequences producing significant alignments:                         (bits)  Value

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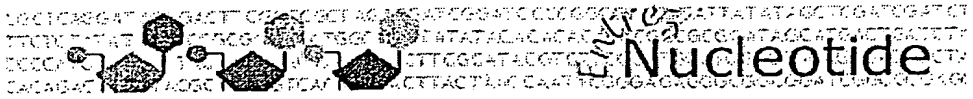

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  TITLE     Direct Submission
  JOURNAL   Unpublished
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  TITLE     Direct Submission
  JOURNAL   Submitted (29-FEB-2000) Production Sequencing Facility, DOE Joint
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            Drive, Walnut Creek, CA 94598, USA
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            Drive, Walnut Creek, CA 94598, USA
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